

## The Origin of Membrane Proteins

Andrew Pohorille and Michael A. Wilson

Membrane proteins mediate functions that are essential to all cells. These functions include transport of ions, nutrients and waste products across cell walls, capture of energy and its conversion into a chemically usable form, transmission of environmental signals to the cell, cellular growth and cell volume regulation. Considering that contemporary membrane proteins are large and complex, both structurally and functionally, a question arises how their much simpler ancestors could have emerged and perform functions in early protobiological evolution. Remarkably, despite their overall complexity, structural motifs in membrane proteins are quite simple, with  $\alpha$ -helices being most common. This suggests that these proteins might have evolved from simple building blocks. To explain how these blocks could have organized into functional structures, we performed large-scale computer simulations of folding peptides at a water-membrane interface, their insertion into the membrane, self-assembly into higher-order structures and function. The results of these simulations, combined with analysis of experimental data led to the first integrated view of the origin and early evolution of membrane proteins. We have shown that peptides with the amino acid sequence such that they can form  $\alpha$ -helices, in which hydrophobic and hydrophilic residues are located at opposite faces readily fold at water-membrane interface. Such helices are called amphiphatic and are quite common among membrane proteins. The specific identity of amino acids appears to be less important. This is a desirable protobiological property because neither a precise protein synthesis mechanism nor the full suite of amino acids was required for the formation of amphiphatic helices. Considering that these helices had to fulfill only very modest sequence constraints, their presence in the protocellular environment should not have been rare. The peptides folded at the interface could have become inserted into the membrane such that they spanned the lipid bilayer. While the insertion of an  $\alpha$ -helix into a membrane is unfavorable, stability can be regained by specific recognition and association of peptides into larger assemblies, such as ion-transporting channels. In contrast to folding and insertion, helix association is strongly sequence-dependent. This feature was probably one of the selection mechanisms operating on protocellular transmembrane peptides. We argue that the emergence of ion channels, required for an early evolution of transport mechanisms, was protobiologically plausible. We show that, despite their simple structure, ion channels could possess properties that, at the first sight, appear to require markedly larger complexity. Conveniently for evolution, properties of these simple proteins can be subtly modulated by local modifications to the sequence rather than global changes in molecular architecture.